Effect of Anapriline on the Conductivity of the Vascular Bed

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The effect of anapriline on the blood flow-pressure relationship is assessed for stepwise changes in the rate of perfusion of the vessels in the hind quarter of the cat body. It is demonstrated that when the synthesis of endothelium-relaxing factor is inhibited, the effect of anapriline is changed, and the augmentation of flow-dependent vasodilation is replaced by vasoconstriction, which increases with the increase in the blood flow through the vessel.

Key Words: *vasodilation; anapriline; β-adrenoblockers; endothelium-relaxing factor; volume blood flow*

The hypotensive effect of anapriline is due not only to a decrease in cardiac output but also to a reduction in peripheral vascular resistance [1,2,5]. It has been shown that nonselective β-adrenoblockers modulate endothelial secretory function and release endothelium-relaxing factor (ERF) [6]. It can be hypothesized that the vadodilating effect of anapriline is observed in cases where the ability of the preparation to stimulate (either directly or indirectly) the release of ERF prevails over its vasoconstricting effect induced by blockade of β-adrenoreceptors of vascular smooth muscles. The present study was undertaken to test this hypothesis.

MATERIALS AND METHODS

Experiments were performed on 18 male cats weighing 2.5-4 kg, anesthetized intraperitoneally with urethane (800 mg/kg) and sodium oxybutyrate (800 mg/kg) under conditions of curarization and artificial ventilation. Autoperfusion of blood vessels of the hind quarter of the body was performed as described elsewhere [3,4] using a pump with regulated output. Arterial pressure in the carotid artery, heart rate (HR), and input perfusion pressure were monitored. The properties of the vessels were assessed from the blood flow-pressure relationship obtained for stepwise changes in perfusion flow rate [3]. Augmentation of the perfusion pressure in re-

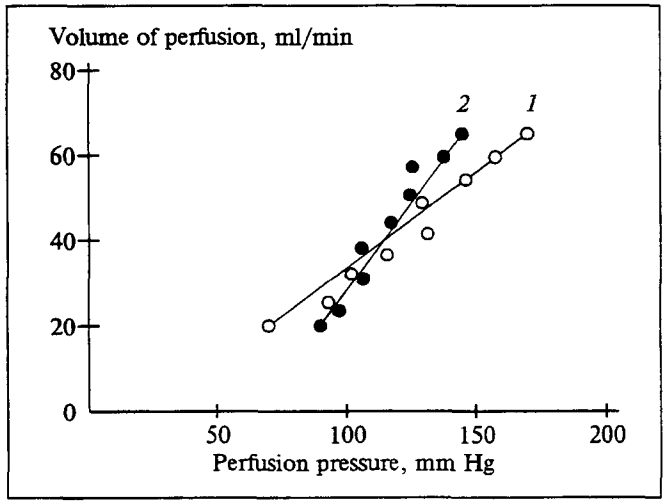

Fig. 1. Effect of anapriline on the blood flow–pressure relationship in the hind quarter of the cat body (results of one experiment). Before (*1*) and after (*2*) administration of anapriline in a dose of 0.5 mg/kg. Each relationship is approximated according to the results of nine–step changes in the volume of perfusion.

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sponse to the same increase in the perfusion rate (prior to and after it), alteration of hydraulic vascular resistance (HVR), and parameter γ, which reflects the correspondence of the vessel's properties to those of a linear hydraulic conductor were analyzed. This parameter shows that in response to an increase in perfusion rate the perfused vessels diminish ($\gamma<0$), do not change ($\gamma=0$), or elevate ($g>0$) their HVR. Thus, comparison of γ before and after a stimulus allows one to assess the degree of vascular dilatation (or constriction) for a flow rate augmentation equal to the initial value. Calculation of γ from a mathematical model for analysis of the blood flow-pressure relationship was described previously [3].

In 12 experiments all parameters were evaluated before and after intravenous injection of 0.5 mg/kg anapriline. In 6 experiments the cats were pretreated with the blocker N^G-nitro-L-arginine in a dose of 5 mg/kg intravenously, and then were given 0.5 mg/kg anapriline.

The results were analyzed using the sign test and Student's paired test; the difference was considered to be significant at $p<0.05$.

RESULTS

The baseline arterial pressure was 104±6 mm Hg, and HR was 172±9 beats/min. When in the first series of experiments the perfusion rate was raised from 19±1 to 68±4 ml/min, the perfusion pressure increased from 66.9±6.4 to 162.5±17.6 mm Hg ($p<0.05$). HR significantly decreased, and γ was less than zero (Table 1). Thus, the steady-state diameter of arteries increased with the flow rate rise, which prevented elevation of the perfusion pressure.

Anapriline significantly lowered arterial pressure (to 85±6 mm Hg), induced bradycardia (HR decreased to 134±8 beats/min) and increased HVR

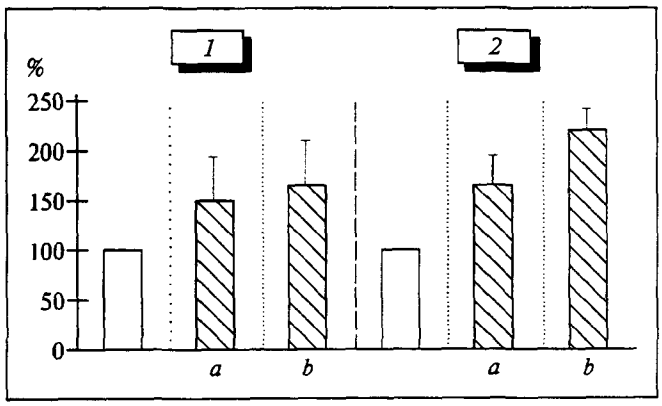

Fig. 2. Changes in intravascular pressure in the hind quarter of the cat body perfused with various blood volumes after treatment with 5 mg/kg N^G-nitro-L-arginine (*a*) followed by administration of 0.5 mg/kg anapriline (*b*). *1*) changes in perfusion pressure at a flow rate of 10.0±1.0 ml/min, *2*) flow rate 47.4±1.1 ml/min. White bars: baseline values taken as 100%, shaded bars: values obtained after administration of the preparations.

at minimal perfusion (Table 1). As the volume of perfusion was increased, the degree of augmentation of HVR dropped, and for the maximum flow rate a decrease in HVR was noted in 5 out of 12 observations (Fig. 1). It can be seen from Table 1 that under the action of anapriline γ decreased considerably, which accounts for the smaller augmentation of the perfusion pressure in response to the flow rate increase. Thus, anapriline induced vasoconstriction for small perfusion volumes and simultaneously increased vascular elasticity.

Administration of N^G-nitro-L-arginine elevated arterial pressure to 123±7 mm Hg, with HR remaining unchanged and HVR tending to decline from 10.0±1.0 to 47.4±1.1 ml/min as the volume of perfusion increased, and γ being less than zero (Table 1). However, the augmentation of the perfusion pressure in response to the increased flow rate after administration of N^G-nitro-L-arginine was greater than before it (Fig. 2).

TABLE 1. Effect of Anapriline and N^G-nitro-L-arginine on Regional Hemodynamics for Altered Flow Rate upon Perfusion of Vascular Bed of Hind Quarter of the Cat Body

Period of study	HVR upon perfusion with blood volume, arb. units		Maximum augmentation of perfusion pressure for increased perfusion volume, mm Hg	Degree of vascular dilation upon increased perfusion volume (γ)
	minimal	maximal		
Before administration of anapriline	3.6±0.3	2.4±0.2	95±13	−0.66±0.05
After administration of anapriline	4.4±0.3*	2.3±0.2	74±11*	−1.74±0.25*
Before administration of N^G-nitro-L-arginine	4.0±0.3	2.7±0.3	86±12	−0.54±0.16
After administration of N^G-nitro-L-arginine	6.0±1.3*	4.3±0.6*	144±11*	−0.33±0.16*
After administration of anapriline	6.5±1.3	5.5±0.7*	194±16*	−0.09±0.11*

Note. Asterisk indicates significance of differences according to the sign test.

After blockade of ERF synthesis, anapriline, caused an insignificant decrease in arterial pressure (to 108±14 mm Hg) and in HR (to 160±13 beats/min). Augmentation of the perfusion pressure in response to the flow rate rise increased considerably. HVR increased for all test volumes of perfusion, the increase being greater for the maximum perfusion pressure (Table 1, Fig. 2). The value of γ did not differ significantly from zero, indicating that the properties of perfused vessels had become more similar to those of a linear hydraulic conductor and that the vessels' ability to stabilize intravascular pressure in response to increased blood flow had declined.

Our results indicate that the effect of anapriline on the elasticity of the vascular bed changes considerably when the synthesis of ERF is inhibited. Increased flow-dependent vasodilation is replaced by vasoconstriction, which is intensified by an increase in the volume of perfusion. Thus, the stimulation of the release of ERF by anapriline is probably important regarding the effect of the preparation on the conductance of the vascular bed and is a component of its hypotensive effect.

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